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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,695	11/24/2003	Joseph L. Wooters	22058-536 (AM101268)	8353

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EXAMINER

ARCHIE, NINA

ART UNIT	PAPER NUMBER
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1645

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/722,695

Applicant(s)

WOOTERS ET AL.

Examiner

Nina A. Archie

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 38-67 is/are pending in the application.
- 4a) Of the above claim(s) 45-67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 38-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/13/2005, 12/19/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statements filed on 1/13/2005 and 12/19/2006 have been considered. Initialed copies are enclosed.

Election/Restrictions

Applicant's election of Group I claims 38-61 and election of species an antibody that binds to cyclophilin A are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 45-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group II (claims 62-67) or a nonelected species (claims 45-61), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in reply filed on 1/16/2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 38-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabled for any method for treating or preventing a Chlamydia infection in a subject, the method comprising administering to a subject in need thereof an effective amount of a therapeutic agent that disrupts the interaction between cyclophilin and a cyclophilin binding partner.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

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The breadth of the claims. The claim is very broad and the therapeutic agent being used to administer to a subject is directed to all antibodies with specificity to cyclophilin A. Furthermore the claims are drawn to a method of treating or preventing a Chlamydia infection. Therefore it is hard for one skilled in the art to determine if all antibodies specific for cyclophilin A can be used in treating or preventing a Chlamydia infection in a subject. The quantity of experimentation required to practice the invention as claimed would require in vivo and in vitro studies of the antibody that is specific for cyclophilin A, the detection antibodies each specific for an epitope which induce an immune response, and further whereby treatment and prevention effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for the treatment or prevention of Chlamydia infection comprising administering a therapeutic agent which is an antibody specific for cyclophilin A to a subject and since determination of these factors for a particular antibody for the particularly claimed conditions, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Nature of the invention. The claims are drawn to methods for treating or preventing a Chlamydia infection in a subject, comprising administering to a subject in need thereof an effective therapeutic agent amount of a therapeutic agent that disrupts the interaction between cyclophilin and a cyclophilin binding partner.

The specification discloses in Example 1 (see pp. 32-33), the presence of cyclophilin A in the elementary bodies of *C. pneumoniae* and *C. trachomatis*. Example 2 and 4 (see pg. 32-33) discloses the binding affinities the cyclophilin-binding polypeptides to magnetic beads coated with cyclophilin A and binding of some recombinant Chlamydia proteins to the cyclophilin A immobilized on a substrate. Example 3 (see pg. 33) discloses crosslinking complexes of cyclophilin A and one or more Chlamydia protein. Example 5 (see pg. 33) discloses limited in vitro data that demonstrate the ability of anti-cyclophilin A antibodies to block Chlamydia infection of human cells.

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The state of the prior art. The state of the art indicate that Chlamydia have a complex life cycle and that elementary bodies enters into the cell by mechanisms unknown, and also through unknown signals, whereby reticulate bodies reconvert to elementary bodies (see Engel 2004 National Academy of the Sciences of USA Vol. 101, No. 27 pgs. 9947-9948 in its entirety). The state of the art indicate that "to be an effective treatment for a Chlamydia infection, an antimicrobial agent must penetrate four membrane layers: (1) the host cell plasma membrane; (2) the inclusion membrane; (3) the Chlamydia outer membrane; and (4) the Chlamydia cytoplasmic membrane" (see Schaechter et al 1999 Mechanisms of Microbial Diseases Third Edition pgs. 266 column 1). The state of the shows an in vitro and in vivo study of administering 2 different monoclonal antibodies (anti-L3T4+ and anti-Lyt-2+). The treatment with anti-L3T4 in vivo and in vitro had no effect on protection of Chlamydia. However the anti-Lyt-2 monoclonal dramatically reduced infection in vivo, however in vitro, the complement was necessary to observe the effect, since the treatment of primed cells with anti-Lyt-2 monoclonal antibody alone was not able to abrogate protection (see Gatel et al 1992 Immunology Vol. 77 pgs. 284-288 especially abstract and pg. 286). The state of the art show that monoclonal antibodies recognizing MOMP (major outer membrane protein) specific epitopes were shown to passively transfer immunity to mice infected with *C. muridarum* in a mouse model for human genital tract infection and also to protect mice pregnant mice from *C. abortus*-induced abortion (Longbottom et al 2006 The Veterinary Journal Vol. 171 pg. 263 see abstract see pg. 267 column 1 paragraph 2). The state of the show that monoclonal antibodies show that recognize monoclonal antibodies neutralized the infectivity of serovar B in an animal, suggesting a functional relationship between antibody-mediated protection of an animal toxicity and chlamydial infectivity (Zhang et al 1989 Infection and Immunity Vol. 57 No. 2 pgs. 636-638 in its entirety).

The state of the art indicates that Chlamydia *trachomatis* have a MIP (macrophage infectivity potentiator) gene that is located in both elementary and reticulate bodies. Furthermore it is noted that the MIP gene of *Chlamydia trachomatis* show strong homology with MIP gene of surface exposed *Legionella pneumophila*. However there are no surface exposed epitopes of the *Chlamydia*

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trachomatis detected therefore it is unlikely that the MIP like protein of *Chlamydia trachomatis* is surface exposed and specific antibodies of the MIP like protein of *Chlamydia trachomatis* are nonneutralizing (see Lundemose et al. 1992 Mol Microbiol. Vol. 6 Issue 17 pgs. 2539-2540). Furthermore the state of the art also show that the *Chlamydia trachomatis* MIP like protein possess peptidyl-prolyl cis-trans isomerases activity (see Lundesome et al 1993 Journal of Bacteriology pg. 3669 column 1) which is identical to cyclophilin including cyclophilin A (see Mann 2001 Natl. Prod. Rep. Vol. 18 pg. 418 column 2 paragraph 1). The art has not shown any antibodies that are specific for cyclophilin A to target cells infected with Chlamydia. The state of the art has not shown any cell surface receptors for Chlamydia that would bind to cyclophilin A. Therefore the art is unpredictable to antibodies that can bind to cyclophilin A and thus target cells infected with Chlamydia which have a complex life cycle.

The state of the art does show immunization with cyclophilin A that inhibits HIV-1 infection, which suggest the possibility that HIV-1 infection could be inhibited by antibodies. The state of the art teaches that cyclophilin A has chemotactic activity and that that the body produces cyclophilin A in response to HIV-1 infection. The art shows that cyclophilin A are recognized by cell surface receptors CD147 on CD4+Tcells (Sherry et al 1998 Proc. Natl. Acad. Sci. USA Vol. 95 pgs. 1758-1763 in its entirety). Therefore the art questions if cyclophilin A is produced in response to a Chlamydia infection how can Chlamydia be prevented by an antibody that is specific for cyclophilin A.

The state of the art indicates that the best approach for controlling the spread of chlamydial infections, in animal and human populations are DNA vaccination (Longbottom et al 2006 The Veterinary Journal Vol. 171 pg. 263 see abstract). The state of the art indicates that vaccination approaches have proved unsuccessful in combating human chlamydial infections (Longbottom et al 2006 The Veterinary Journal Vol. 171 pg. 263 see abstract, pg. 265 column 2 paragraphs 2-4, pg. 266 column 1 paragraph 1). The art shows that if detected early, chlamydial infections are treatable with antibacterial agents (Igietseme et al 2003 Expert Rev. Vaccines Vol. 2 No. 1 see pg. 130). The art discloses defining epitopes is not as easy as it seems. Greenspan et

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al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a particular immune response (i.e. generation of an antibody that binds to a given epitope) can only be identified empirically (Greenspan et al. 1999 Nature Biotechnology 17: 936-937). The art does not teach any antibodies that bind to cyclophilin A to treat a Chlamydia infection. This constitutes undue experimentation. Therefore, given the lack of success in the art. For the reasons set forth supra, the state of the art is unpredictable to antibodies that can bind to cyclophilin A to treat infection and have limitations with regard to complex life cycle of Chlamydia, the unknown mechanism of elementary bodies entering into the cell, the unknown signals whereby reticulate bodies reconvert to elementary bodies and the limitations of the treatments of administering antibodies to a subject.

Guidance in the specification. The specification fails to describe immunoepitopes against which the claimed antibodies are raised and must subsequently bind. The specification is silent as to what specific "immunoepitope" meets the limitations of the claims. Additionally, the specification is silent with regard to what epitopes are cross-reactive. There is no showing in the specification that the antibody that binds to cyclophilin A can be used to treat or prevent Chlamydia infection. The only information regarding antibodies is that they are capable of binding and they have the ability to block Chlamydia infection. The specification has not shown any antibodies that are specific for cyclophilin A to target cells infected with Chlamydia nor has the specification shown any cell surface receptors for Chlamydia that would bind to cyclophilin A. There is not empirical data reported on the specification at the time of filing showing efficacy of a therapeutic agent (i.e. antibody that binds specifically to cyclophilin A). Therefore the

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specification fails to describe any antibodies that specifically bind to cyclophilin A in the treatment or prevention of a Chlamydia infection.

Working examples. The specification does not give any working example (i.e. challenged mice models or passive immunization approaches).

In conclusion, the claimed inventions are not enabled for a method of treating or preventing a Chlamydia infection in a subject, comprising administering to a subject in need thereof an effective amount of a therapeutic agent that disrupts the interaction between cyclophilin between cyclophilin and a cyclophilin binding partner. The claim is directed all antibodies with specificity to cyclophilin A. The state of the art teaches that although it *Chlamydia trachomatis* have a MIP (macrophage infectivity potentiator) like protein that posses peptidyl-prolyl cis-trans isomerase activity which is identical to cyclophilins like protein, it is poorly exposed. The state of the art teaches that the best approach for controlling the spread of chlamydial infection is vaccination, which have proved to have limitations. Furthermore the state of the art is unpredictable and does not teach any antibodies that bind to cyclophilin A to treat or prevent a Chlamydia infection. There is a lack of working examples. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 38, the independent claim recites the phrase "interaction". However, neither the claim nor the specification clearly defines nor sets forth the meaning or means to assess "interaction". Therefore, the skilled artisan would not be readily apprised of the metes and bounds of "interaction" nor how to assess such. It is unclear how to interpret "interaction" inasmuch as it is not a recognized term and not defined in the specification.

Status of the Claims

No claims allowed.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Nina A Archie

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Examiner

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REM 3B31

Patricia A. Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER